

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method for producing
N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester,
comprising:

(1) subjecting ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine 1-methyl ester and
3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or ~~derivatives~~ a derivative thereof to
reductive alkylation in a solvent to ~~produce~~ obtain
N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester;
and (2) crystallizing said ~~compound~~

N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester,

wherein said reductive alkylation comprises catalytic hydrogenation, and

wherein said derivative thereof is selected from the group consisting of

3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)-2-propenylaldehyde, and

acetals derived therefrom.

2. (Currently Amended) The method as ~~defined in~~ of Claim 1, wherein the said process
~~for~~ crystallizing said ~~compound~~

N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester

comprises any one of the following crystallization methods:

- a. crystallization with a solvent useful for crystallization;
- b. crystallization after extraction with water; and
- c. crystallization after separation of ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine

1-methyl ester.

3. (Currently Amended) A method for purifying N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester, which comprises:

subjecting a composition which comprises

N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester and comprising at least one compound selected from the group consisting of ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine 1-methyl ester, a peptide derivative, an amino acid, an amino acid derivative, an aldehyde, an acetal and an alcohol derivative as impurity to at least any one of the following crystallization processes:

- a. crystallization with a crystallization solvent;
- b. crystallization after extraction with water; and
- c. ~~in the instance Aspartame is present;~~ when said composition comprises

N-L- α -aspartyl-L-phenylalanine 1-methyl ester, further crystallization after Aspartame said
N-L- α -aspartyl-L-phenylalanine 1-methyl ester has been separated,

to crystallize said compound obtain crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester.

4. (Currently Amended) The method ~~as defined in~~ of Claim 1, wherein ~~the said~~ solvent for ~~the said~~ reductive alkylation reaction is at least one solvent selected from the group consisting of ~~alcohol(s)~~ alcohol(s), tetrahydrofuran, acetonitrile, toluene, acetic acid, ~~and~~ acetic acid ~~ester(s)~~ esters, ~~or a~~ and mixed solvent solvents which ~~consists of~~ comprise at least one of these organic solvents and water.

5. (Currently Amended) The method ~~as claimed in~~ of Claim 2, wherein said ~~compound~~ N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester is crystallized by a process of concentration or by a process for solvent substitution.

6. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein ~~the~~ said solvent for said crystallization of ~~said compound~~ N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester is at least one solvent selected from the group consisting of ~~alcohol(s)~~ alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, and acetic acid ester(s) esters, ~~or a~~ and mixed solvent solvents which ~~consists of~~ comprise at least one of these organic solvents and water.

7. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein ~~the~~ said solvent for said crystallization of ~~said compound~~ N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester ~~comprises a~~ is the same solvent which has been used in the reductive alkylation reaction.

8. (Currently Amended) The method ~~as claimed in~~ of Claim 5, wherein ~~the solvent of the substitution aspect of crystallization is~~ said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester is crystallized by solvent substitution using at least one solvent selected from the group consisting of ~~alcohol(s)~~ alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, and acetic acid ester(s) esters, ~~or a~~ and mixed solvent solvents which ~~consists of~~ comprise at least one of these organic solvents and water.

9. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein ~~the~~ said solvent of ~~the~~ said reductive alkylation reaction is ~~alcohol(s)~~ one or more alcohols or a mixed solvent of ~~alcohol(s)~~ one or more alcohols and water, and the solvent of ~~the~~ said crystallization ~~process~~ of ~~the compound~~ said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester is ~~alcohol(s)~~ one or more alcohols or a mixed solvent comprising ~~alcohol(s)~~ one or more alcohols.

10. (Currently Amended) The method ~~as claimed in~~ of Claim 2, wherein ~~the solvent~~
~~of crystallization~~ said

N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
is crystallized after extraction with water is using at least one solvent selected from the group
consisting of ~~alcohol(s)~~ alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic
acid, ~~and acetic acid ester(s)~~, and ~~or a mixed solvent~~ solvents which ~~consists of~~ comprise at
least one of these organic solvents and water.

11. (Currently Amended) The method ~~as claimed in~~ of Claim 2, wherein said
N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
is crystallized after extraction with water and said ~~the process for~~ extraction with water is
conducted with a mixed solvent which ~~consists of~~ comprises water and one or more organic
solvent(s) solvents, wherein said ~~the~~ organic solvent ~~forming~~ forms a layer which separates
from an aqueous layer upon mixture with water, and said
N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
~~being~~ is extracted into the aqueous layer.

12. (Currently Amended) The method ~~as claimed in~~ of Claim 11, wherein said organic
solvent(s) solvent is at least one solvent selected from the group consisting of acetic acid ester(s)
esters, ether, chloroform, dichloromethane, hexane, toluene, ~~alcohol(s)~~ alcohols,
tetrahydrofuran, acetone, acetonitrile and acetic acid.

13. (Currently Amended) The method ~~as claimed in~~ of Claim 2, wherein ~~the solvent~~
~~for said crystallization~~ said
N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
is crystallized after having separated ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine 1-methyl
ester and is crystallized from is at least one solvent selected from the group consisting of
~~alcohol(s)~~ alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, ~~and~~ acetic

acid ester(s) esters, or a and mixed solvent solvents which ~~consists of~~ comprise at least one of these organic solvents and water.

14. (Currently Amended) The method ~~as claimed in~~ of Claim 2, wherein said process for separating ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine 1-methyl ester is a process for separating ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine 1-methyl ester by crystallization or precipitation with at least one solvent selected from the group consisting of acetic acid ~~ester(s)~~ esters, ether, chloroform, dichloromethane, hexane, toluene, ~~alcohol(s)~~ alcohols, tetrahydrofuran, acetone, acetonitrile, acetic acid and water.

15. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein said reductive alkylation reaction is conducted in ~~the presence of hydrogen and a catalyst for reductive alkylation, and the solvent for said reaction is~~ at least one organic solvent which dissolves the starting materials or a mixed solvent of said organic solvents and water, and when an insoluble material is present in the reaction mixture obtained after said reductive alkylation reaction, said insoluble material is separated by filtration.

16. (Canceled)

17. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein ~~the catalyst for said reductive alkylation reaction is a~~ said catalytic hydrogenation ~~eatalyst and is conducted in the presence of~~ at least one catalyst selected from the group consisting of palladium, platinum, and rhodium based catalysts.

18. (Currently Amended) The method ~~as claimed in~~ of Claim 1 ~~45~~, wherein said catalytic hydrogenation is conducted at a hydrogen ~~is present at a~~ pressure of 0.1 to 1 MPa.

19. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein, ~~in~~ said reductive alkylation reaction, ~~the reaction is conducted at a~~ temperature ranges range of from 15 to 50 °C, and ~~the a~~ reaction time ranges of from 2 to 48 hours.

20. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein ~~the pH of the reaction solvent for said reductive alkylation reaction ranges~~ is carried out in a reaction solvent having a pH of from 4 to 6.5.

21. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein the molar ratio of ~~the Aspartame~~ said N-L- α -aspartyl-L-phenylalanine 1-methyl ester to said 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or derivative thereof ranges from 0.5 to 2.

22. (Currently Amended) The method ~~as claimed in~~ of Claim 3, wherein said aldehyde is selected from the group consisting of:

3-(3-methoxy-4-hydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,

3-(3-methoxy-4-protectedhydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-protectedhydroxyphenyl)-2-propenylaldehyde,

and said acetal comprises any acetal derived from these aldehydes.

23. – 28. (Canceled)

29. (Currently Amended) The method ~~as claimed in~~ of Claim 1, wherein said 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde or derivative thereof is prepared by subjecting 3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde or an acetal thereof, wherein the hydroxyl group may be protected, to reduction to ~~reduce the double bond of the compound~~ obtain said 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde or derivative thereof.

30. (Currently Amended) The method ~~as defined in~~ of Claim ~~28~~ 29, wherein said ~~process for~~ reduction is conducted in the presence of a reduction catalyst or a rhodium based catalyst.

31. (Currently Amended) The method ~~as claimed in~~ of Claim 3, wherein said ~~compound~~ N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine

1-methyl ester is crystallized by a process of concentration or by a process for solvent substitution.

32. (Currently Amended) The method ~~as claimed in~~ of Claim 3, wherein ~~the solvent for said~~ crystallization of said ~~compound~~

N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester is carried out in at least one solvent selected from the group consisting of ~~alcohol(s)~~ alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, and acetic acid ~~ester(s)~~ esters, ~~or a~~ and mixed solvent solvents which ~~consists of~~ comprise at least one of these organic solvents and water.

33. (Currently Amended) The method ~~as claimed in~~ of Claim 2, wherein ~~the solvent for said~~ crystallization of said ~~compound~~ ~~comprises~~

N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester is carried out in the same a solvent which has been used in the said reductive alkylation reaction.

34. (Currently Amended) The method ~~as claimed in~~ of Claim 31, wherein ~~the said~~ N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester is crystallized by solvent ~~of the substitution aspect of crystallization is using~~ at least one solvent selected from the group consisting of ~~alcohol(s)~~ alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, and acetic acid ~~ester(s)~~ esters, ~~or a~~ and mixed solvent solvents which ~~consists of~~ comprise at least one of these organic solvents and water.

35. (Currently Amended) The method ~~as claimed in~~ of Claim 2, wherein ~~the said~~ solvent of the reductive alkylation reaction is ~~alcohol(s)~~ one or more alcohols or a mixed solvent of ~~alcohol(s)~~ one or more alcohols and water, and the solvent of the crystallization process of the compound said

N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester

is ~~alcohol(s)~~ one or more alcohols or a mixed solvent comprising ~~alcohol(s)~~ one or more alcohols.

36. (Currently Amended) The method ~~as-claimed in~~ of Claim 3, wherein ~~the solvent~~
~~of crystallization~~ said
N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
is crystallized after extraction with water is using at least one solvent selected from the group
consisting of ~~alcohol(s)~~ alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic
acid, and acetic acid ~~ester(s)~~ esters, or a and mixed solvent solvents which ~~consists of~~ comprise
at least one of these organic solvents and water.

37. (Currently Amended) The method ~~as-claimed in~~ of in Claim 3, wherein said
N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
is crystallized after extraction with water and said ~~the process for~~ extraction with water is
conducted with a mixed solvent which ~~consists of~~ comprises water and one or more organic
solvent(s) solvents, wherein said the organic solvent ~~forming~~ forms a layer which separates
from an aqueous layer upon mixture with water, and said
N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
being is extracted into the aqueous layer.

38. (Currently Amended) The method ~~as-claimed in~~ of Claim 3, wherein ~~the solvent~~
~~for said crystallization~~ said
N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester
is crystallized after having separated ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine 1-methyl
ester and is crystallized from is at least one solvent selected from the group consisting of
~~alcohol(s)~~ alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, and acetic
acid ~~ester(s)~~ esters, or a and mixed solvent solvents which ~~consists of~~ comprise at least one of
these organic solvents and water.

39. (Currently Amended) The method ~~as claimed in~~ of Claim 3, wherein said process for separating ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine 1-methyl ester is a process for separating ~~Aspartame~~ N-L- α -aspartyl-L-phenylalanine 1-methyl ester by crystallization or precipitation with at least one solvent selected from the group consisting of acetic acid ~~ester(s)~~ esters, ether, chloroform, dichloromethane, hexane, toluene, ~~alcohol(s)~~ alcohols, tetrahydrofuran, acetone, acetonitrile, acetic acid and water.